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| 09/800,520 | 03/08/2001 | Hideo Iba | 423-59 | 5027 |

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| EXAMINER | |
|---|---|
| LEFFERS JR, GERALD G | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1636 | |

DATE MAILED: 05/19/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 09/800,520 | IBA ET AL. | |
| | Examiner | Art Unit | |
| | Gerald G Leffers Jr., PhD | 1636 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *04 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *34-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/4/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

## DETAILED ACTION

Receipt is acknowledged of an amendment, filed 2/14/2004, in which claims were amended (claims 34-35, 39-40, 44-45) and in which new claims were added (claims 46-57). Claims 34-57 are pending in the instant application.

Any rejection of record in the previous office action not addressed herein is withdrawn. As applicants' amendment of the claims in the response filed 2/14/2004 has necessitated the new grounds of rejection made herein, this action is FINAL.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 34-57 are is rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new rejection necessitated by applicants' amendment of the claims in the response filed 2/14/2004.**

Claims 34-57 are directed to a broad class of vectors and methods of use thereof to express desired genes in a given cell. At least two of the claims are directed to use of the vectors in gag/pol expressing cells. In the specification, however, the short-lived transcript drug resistance genes are only described in the context of selecting cells comprising very specific

expression constructs (e.g. construct A, pages 8-12) integrated into the host cell genome for the purpose of preparing pre-packaging cells useful for the preparation of retroviral gene transfer vectors (e.g. pages 16-17, bridging paragraph; page 22, 1st paragraph). No broader use for the recited short-lived transcript drug resistance genes is contemplated in the originally filed specification or claims. Thus, the broader scope of use encompassed by the rejected claims is impermissible NEW MATTER.

***Response to Arguments***

Applicant's arguments filed in the response of 2/24/2004 have been fully considered but are deemed unpersuasive. The response essentially argues: 1) the specification broadly describes use of a deteriorated drug-resistance gene in contexts other than construct A and transfer into cell types other than packaging cells and such description is explicit at several places in the specification (e.g. pages 7-8; pages 16-17 and pages 36-37), 2) applicants taught that, in general, cells requiring expression of a stronger resistance marker can be obtained from a drug-resistance gene in which the mRNA transcript of that gene has been destabilized and have exemplified an embodiment where a high expression of a foreign gene product was obtained (i.e. VSV-G protein).

Each of the passages cited in applicants' response was solely directed to the use of the short-lived transcript drug-resistance gene in the context of the prepackaging cells of the invention (e.g. construct A used to express a viral structural gene such as VSV-G). For example, in the first passage cited by the response, the inventors teach "[The present inventors] have also utilized the phenomenon that, in the preparation of the above-mentioned prepackaging cells, cells requiring the expression of a stronger resistance marker can be efficiently screened by using a

drug resistance marker gene one the function of which has been deteriorated..." (examiner's emphasis added). The second passage cited by applicants is present at the bridging paragraph for pages 16-17 of the instant specification. Read in the context of the paragraph preceding the cited passage, it is clear that the phrase "As the drug resistance gene..." at the beginning of the cited passage directs the teachings of the passage to the use of the modified drug-resistance gene in the context of preparing the prepackaging cells of the invention. The teachings with regard to the nature of the modified drug resistance gene are clearly only intended for use in the prepackaging constructs of the invention and are not taught for use in a broader context. Finally, the experiment described with regard to selection of cells expressing high levels of VSV-G utilize a vector meeting the limitations of construct A as described in the specification (e.g. page 14, last paragraph). For example, a construct comprising, in order, a promoter, recombinase recognition sequence, a drug resistance gene, a polyA addition signal, the recombinase recognition sequence, the viral structural gene (e.g. a gene encoding VSV-G for pseudotyping of retroviral virions) and a polyA addition signal. The passage cited by applicants clearly indicates the expression of the viral structural gene encoding VSV-G only after addition of the Cre recombinase to excise the fragment encoding the modified drug-resistance gene. Thus, the third passage cited in the response is directed explicitly to a vector meeting the limitations of construct A of the invention and is not representative of a broader teaching of vectors other than construct A or construct B for expressing a foreign gene.

Claims 35-40 and 47-52 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter that was

not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This rejection is maintained for reasons of record in the previous office action and which are repeated below.**

The rejected claims comprise the limitation "...wherein said expression vector confers drug resistance when transfected into a cell and the drug resistance gene is transcribed at a higher rate under selection with the drug because of the presence of the mRNA-destabilizing sequence." This limitation specifies that the presence of the short-lived transcript drug resistance marker *necessarily* confers on the expression vector an increased expression of a desired gene. There is no literal support for this concept in the specification. The specification provides support for *selection* from a larger population of cells comprising the construct A, a subpopulation wherein the expression of the short-lived transcript is elevated above the remaining population. Therefore, the cited limitation is impermissible NEW MATTER.

***Response to Arguments***

Applicant's arguments filed in the response of 2/24/2004 have been fully considered but are deemed unpersuasive. The response essentially argues: 1) an amendment introducing an inherent characteristic of a product into the claims is not prohibited by the written disclosure requirement, 2) the specification teaches use of an expression vector for a foreign gene comprising a short-lived transcript drug-resistance gene in which the same promoter transcribes the foreign gene and the drug-resistance gene, 3) high-rate transcription by the promoter due to the present of the mRNA-destabilizing sequence is implicit in the teaching of such drug-selected cells, 4) it is implicit that the use of mRNA-destabilizing sequences that the promoter

transcribing the drug-resistance gene and the foreign gene is activated by insertion in the cell's genome, 5) the promoter is activated to transcribe at a high rate to compensate for destabilization of the short-lived transcript of the drug-resistance gene and only the cell with this promoter survives, 6) all of which is consistent with the teachings of the specification at page 9, "Differences in gene expression for the constructs taught in the specification appear to be due to the location of insertion of the targeting vector in the specification and not due to some structural aspect of the claimed vector itself." (examiner's emphasis added).

The examiner agrees that it is not new matter to amend the claims to recite a characteristic that is inherent to the product claimed. It is the examiner's contention that the cited limitation specifies that the presence of the short-lived transcript drug resistance marker *necessarily* confers on the expression vector an increased expression of a desired gene. The examiner understands that based upon the site of integration of the expression construct into the host genome there arises different levels of transcriptional activity for the sequences operatively linked to the promoter of the construct (e.g. the modified drug-resistance gene and/or the gene of interest). Thus, the specification provides support for *selection* from a larger population of cells comprising the construct, a subpopulation wherein the expression of the short-lived transcript is elevated above the remaining population due to the positional effects of insertion on transcription. As indicated above by the teachings of the instant specification, the enhanced level of expression is not *directly* due to some structural aspect of the claimed vector itself, as is implied by the limitation "...wherein said expression vector confers drug resistance when transfected into a cell and the drug resistance gene is transcribed at a higher rate under selection with the drug because of the presence of the mRNA-destabilizing sequence.". The short-lived

transcript drug resistance gene merely provides a means for selecting those insertion events that lead to high levels of expression due to the insertion location. Therefore, there remains no literal support in the specification as filed for the cited phrase.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 34-57 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. **This is a new rejection.**

Claims 34-57 are vague and indefinite in that the metes and bounds of the terms "foreign gene" or "foreign gene product" are unclear. The terms are not clearly described in the specification and it is unclear with regard to what the gene or gene product is supposed to be foreign. It would be remedial to amend the claim language to clearly indicate what is intended by the cited terms.

### *Conclusion*

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (571) 272-0772. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

GERRY LEFFERS
PRIMARY EXAMINER